DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96M–0311]

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Agency Information Collection Activities; Submission for OMB Review; Comment Request; Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that the proposed collection of information listed below has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995 (the PRA).

DATES: Submit written comments on the collection of information by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit written comments on the collection of information to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Wendy Taylor, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: JonnaLynn P. Capezzuto, Office of Information Resources Management (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4659.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

PHS Guideline on Infectious Disease Issues in Xenotransplantation

The statutory authority to collect this information is provided under sections 351 and 361 of the PHS Act (42 U.S.C. 262 and 264) and the provisions of the Federal Food, Drug, and Cosmetic Act that apply to drugs (21 U.S.C. 301 *et seq.*). This PHS guideline is revised based on public comment to a previous document entitled ''Draft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation (August 1996),'' which published in the **Federal Register** of September 23, 1996 (61 FR 49919). The PHS guideline recommends procedures to diminish the risk of transmission of infectious agents to the xenotransplantation product recipient and the general public. The PHS guideline is intended to address public health issues raised by xenotransplantation, through identification of general principles of prevention and control of infectious diseases associated with xenotransplantation that may pose a hazard to the public health. The collection of information described in this guideline is intended to provide general guidance to sponsors in: (1) The development of xenotransplantation clinical protocols, (2) the preparation of submissions to FDA, and (3) the conduct of xenotransplantation clinical trials. Also, the collection of information will help ensure that the sponsor maintains important information in a cross-referenced system that links the relevant records of the xenotransplantation product recipient, xenotransplantation product, source animal(s), animal procurement center, and significant nosocomial exposures. The PHS guideline describes an occupational health service program for the protection of health care workers involved in xenotransplantation procedures, caring for xenotransplantation product recipients, and performing associated laboratory testing. The PHS guideline also describes public health needs for: (1) A pilot national xenotransplant data base, which is currently under development by PHS; (2) a central PHS biologic specimen archive; and (3) the Secretary's Advisory Committee on Xenotransplantation, which is being developed and implemented by the Department of Health and Human Services. These public health programs and this PHS guideline are intended to protect the public health and help ensure the safety of

using xenotransplantation products in humans by preventing the introduction, transmission, and spread of infectious diseases associated with xenotransplantation.

Respondents to this collection of information are the sponsors of clinical studies of investigational xenotransplantation products under investigational new drug applications (IND's) and xenotransplantation product procurement centers, referred to as source animal facilities. Currently, there are 11 respondents who are sponsors of IND's, which include protocols for xenotransplantation in humans. Other respondents for this collection of information are 18 source animal facilities which provide source xenotransplantation product material to sponsors for use in human xenotransplantation procedures. These 18 source animal facilities keep medical records of the herds/colonies as well as the medical records of the individual source animal(s).

The PHS guideline proposes that certain specimens and records be maintained for 50 years beyond the date of the xenotransplantation. These include: (1) Records linking each xenotransplantation product recipient with relevant health records of the source animal, herd or colony, and the specific organ, tissue, or cell type included in or used in the manufacture of the product (3.2.7.1); (2) aliquots of serum samples from randomly selected animal and specific disease investigations (3.4.3.1); (3) source animal biological specimens designated for PHS use (3.7.1); animal health records (3.7.2), including necropsy results (3.6.4); and (4) recipients' biological specimens (4.1.2).

The retention period is intended to assist health care practitioners and officials in surveillance and in tracking the source of an infection, disease, or illness that might emerge in the recipient, the source animal, or the animal herd or colony after a xenotransplantation. Although the draft PHS guideline discussed holding specimens and records indefinitely, comments described this recommendation as impractical and unfeasible.

The recommendation for maintaining records for 50 years is based on clinical experience with several human viruses that have presented problems in human-to-human transplantation and are therefore thought to share certain characteristics with viruses that may pose potential risks in

xenotransplantation. These characteristics include long latency periods and the ability to establish persistent infections. Several also share the possibility of transmission among individuals through intimate contact with human body fluids. Human immunodeficiency virus (HIV) and Human T-lymphotropic virus (HTLV) are human retroviruses. They contain ribonucleic acid that is reverse-transcribed into deoxyribonucleic acid (DNA) using an enzyme provided by the virus and the cell machinery. That DNA can then be integrated into the cellular DNA. Both viruses establish persistent infections and have long latency periods before the onset of disease, 10 years and 40 to 60 years, respectively. The human hepatitis viruses are not retroviruses, but several share with HIV the characteristic that they can be transmitted through body fluids, can establish persistent infections, and have long latency periods (e.g., approximately 30 years for Hepatitis C).

In addition, the PHS guideline recommends that a record system be developed that allows easy, accurate, and rapid linkage of information among the specimen archive, the recipient's medical records, and the records of the source animal for 50 years. If record systems are maintained in a computer data base, electronic backups should be kept in a secure office facility and backup on hard copy should be routinely performed (4.1.2.2). The development of such a record system would be a one-time burden. Such a system is intended to cross-reference and locate relevant records or recipients, source animals and facilities, and specimens of both the recipient and the source animal. Based on agency experience in establishing new, small volume, recordkeeping and tracking systems, we estimate approximately 16 hours would be necessary for each sponsor to set up the records system.

The total annual reporting and recordkeeping burden is estimated to be approximately 343 hours. The burden estimates are based on FDA's records of xenotransplantation-related IND's and estimates of time required to create an appropriate record system and to complete the various reporting and recordkeeping tasks described in the PHS guideline. A total of 22 IND's have been submitted since 1994 resulting in an average of 4 IND submissions per year. A total of 87 patients have been treated over a 3-year period indicating there are on average 29 xenotransplantation

product recipients per year. FDA does not expect the number of clinical studies using xenotransplantation to increase significantly in the next few years; therefore, the agency is using these historical figures in projecting burdens for the next 3 years.

In the **Federal Register** of May 26, 2000 (65 FR 34196), FDA, on behalf of PHS, published a 60-day notice for public comment on the proposed collection of information provisions in the PHS guideline on infectious disease issues in xenotransplantation. FDA received four letters of comment in response to the notice. One of the letters did not provide any comments on the information collection provisions. PHS is responding below to those comments which address information collection issues. Other comments, not related to the proposed information collection provisions, will be considered by PHS in future revisions of the guideline.

Two comments addressed the PHS guideline recommendation that records be retained for 50 years.

(Comment 1) One comment stated that although the need for record retention is very important, the retention of records for 50 years would be an undue burden on a sponsor.

(Comment 2) The other comment stated that, in view of rapidly changing technology that would require conversion of data whenever newer computer systems are acquired, the retention period would constitute an undue burden because of the difficulty of maintaining linked, computerized data throughout this period of time.

The 50-year retention period is intended to assist health care practitioners and public health officials in infectious disease surveillance and in tracking the source of an infection, disease, or illness that might emerge in the xenotransplantation product recipient, the source animal, or the animal herd or colony following xenotransplantation. The recommendation for maintaining records for 50 years is based on clinical experience with several human viruses that have presented problems in human-to-human transplantation and are thought to share certain characteristics with viruses that may pose potential risks in xenotransplantation. These characteristics include long latency periods and the ability to establish persistent infections Several of these human viruses

can also be transmitted among individuals through intimate contact with human body fluids. For example, HIV and HTLV are human retroviruses that establish persistent infections and have long latency periods before the onset of disease, 10 years and 40 to 60 years, respectively. The human hepatitis viruses are not retroviruses, but several share with HIV the characteristic that they can be transmitted through body fluids, can establish persistent infections, and have long latency periods (e.g., approximately 30 years for Hepatitis C).

As new computer data systems are developed, both software and hardware manufacturers typically provide for the transfer or conversion of existing data into a new system. With today's rapidly developing information technology, such transfers and conversions are usual and customary practice. It is the responsibility of the sponsor to ensure that all data are appropriately transferred to, and retrievable from, their new/updated computer systems. Because of the need for the long-term monitoring of the health of xenotransplantation product recipients and source animals, a sponsor should ensure that these data remain compatible with the computerized data systems that will be used during the 50-year retention period.

Two comments addressed the submission of information to a national xenotransplantation data base.

(Comment 3) One comment stated that it would be redundant to maintain records for 50 years and submit the same information to the National Xenotransplantation Database (NXD).

(Comment 4) The other comment stated that it would constitute an additional burden to submit information to the NXD for companies that already submit these data to FDA.

The NXD is not operational, but rather is in a pilot phase at this time. In developing this data base, PHS will make an effort, whenever possible, to avoid the imposition of any redundant or excess paperwork requirements. The public will be offered an opportunity to comment on any information collection burdens associated with the NXD prior to implementation. Sponsors should, however, recognize that they should maintain information that goes beyond what may be proposed for submission to the NXD. Such information includes, for example, personal identifiers that would

enable PHS to contact specific individuals in case of a public health emergency, information on recipient contacts and health care workers, detailed information on the xenotransplantation procedure, and detailed information on husbandry of the source animal. Finally, because sponsors will need to monitor patient health over time, retention of records that are more complete than data submitted to the NXD will be necessary.

(Comment 5) One comment stated that under sections 3.4.1 and 3.4.3.2, all incidents that affect herd or colony health that are recorded by a source animal facility should also be reported to FDA.

PHS agrees that in some cases incidents affecting animal herd or colony health should be reported to FDA. For example, under § 312.32(c)(1)(i)(B) (21 CFR 312.32(c)(1)(i)(B)), a sponsor must notify FDA and all participating investigators of "[a]ny finding from laboratory animals that suggests a significant risk for human subjects * * *" Thus, if a health event in the source herd or colony suggests that recipients of xenotransplantation products from the source animals in that herd/colony may be at significant risk, the health event must be reported to FDA. However, as with any herd of animals, many health events may occur, such as injuries and minor illnesses. These events should be assessed, as appropriate, to determine whether there are any health implications for the xenotransplantation product recipients. Primary responsibility for designing and monitoring the conduct of xenotransplantation clinical trial rests with the sponsor (e.g., 21 CFR 312.23(a)(6)(iii)(*d*) and 312.50). As part of the sponsor's responsibility when filing an IND, procedures should be developed to identify incidents that negatively affect the health of the herd or colony. This information is relevant to the safety review of every xenotransplantation product application. Such information, as well as the procedures to collect the information, should be reported to FDA. PHS has revised the guideline in section 3 to note the requirements for developing such procedures and for submitting the procedures to FDA.

(Comment 6) One comment stated that under section 2.5.7, clinical investigators should report to FDA any serious or unexplained illnesses of xenotransplantation product recipients that are reported to them.

PHS agrees that serious or unexplained illnesses should be reported but they should be reported by the sponsor rather than by the clinical investigator. For example, under § 312.32(c)(1)(i)(A), a sponsor must notify FDA and all participating investigators of any adverse experience associated with the use of an investigational product that is both serious and unexpected. The sponsor is in the best position to evaluate such events and determine the implications of the event for the safety of the xenotransplantation product and any potential impact such product may have on the clinical study.

FDA is requesting OMB approval for the following reporting and recordkeeping recommendations in the PHS guideline, except as noted:

TABLE 1.—REPORTING RECOMMENDATIONS

PHS Guideline Section	Description
3.2.7.2	Notify sponsor or FDA of new archive site when source animal facility or sponsor ceases operations.
3.4	Standard operating procedures (SOP's) of source animal facility should be available to review bodies.
3.5.1	Include increased infectious risk in informed consent if source animal quarantine period of 3 weeks is shortened.
3.5.4	Sponsor to make linked records described in section 3.2.7 available for review.
3.5.5	Source animal facility to notify clinical center when infectious agent is identified in source animal or herd after xenotransplantation product procurement.

TABLE 2.—REPORTING RECOMMENDATIONS

PHS Guideline Section	Description
3.2.3[1]	Procedures to ensure the humane care of animals.
3.2.4[2]	Incorporate procedures consistent with accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International) and consistent with the National Research Council's (NRC's) Guide.
3.2.6[3]	Animal facility SOP's should be described.
3.2.7 and 4.3	Establish records linking each xenotransplantation product recipient with relevant records, including SOP's of animal procurement, facility herd health surveillance, and lifelong health history of source animal. Maintain cross-referenced system that links all relevant records (recipient, product, source animal, animal procurement center, and significant nosocomial exposures).
3.4.2	Document results of monitoring program used to detect introduction of infectious agents which may not be apparent clinically.
3.4.3.2	Document full necropsy investigations including evaluation for infectious etiologies.
3.5.1	Document justification for shortening a source animal's quarantine period of 3 weeks prior to xenotransplantation product procurement.
3.5.2	Document absence of infectious agent in xenotransplantation product if its presence elsewhere in source animal does not preclude using it.
3.5.4	Add summary of individual source animal record to permanent medical record of the xenotransplantation product recipient.
3.6.4	Document complete necropsy results on source animals (50-year record retention).
3.7	Link xenotransplantation product recipients to individual source animal records and archived biologic specimens.
4.2.3.2	Record baseline sera of xenotransplantation health care workers and specific nosocomial exposure.
4.2.3.3 and 4.3.2	Keep a log of health care workers' significant nosocomial exposure(s).
4.3.1	Document each xenotransplant procedure.

TABLE 2.—REPORTING RECOMMENDATIONS—Continued

PHS Guideline Section	Description
5.2	Document location and nature of archived PHS specimens in health care records of xenotransplantation product recipient and source animal.

[1] These procedures are set forth in 9 CFR parts 1, 2, and 3 and the "Public Health Service Policy on Humane Care and Use of Laboratory Animals" (http://www.grants.nih.gov/grants/olaw/references/phspol.htm) and are considered usual and customary practice.
[2] These procedures are set forth in the AAALAC International Rules of Accreditation (http://www.aaalac.org) and the NRC's "Guide for the Care and Use of Laboratory Animals" (1996) and are considered usual and customary practice.
[3] These procedures are set forth in the "Public Health Service Policy on Humane Care and Use of Laboratory Animals" (http://www.grants.nih.gov/grants/olaw/references/phspol.htm) and are considered usual and customary practice.

FDA estimates the burden for this collection of information as follows:

TABLE 3.—ESTIMATED ANNUAL REPORTING BURDEN[1]

PHS Guideline Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
3.2.7.2[2]	18	0	0	0.5	0
3.2.7.2[2]	11	0	0	0.5	0
3.4[3]	11	0.4	4	0.08	0.3
3.5.1[4]	11	0.09	1	0.25	0.25
3.5.4[5]	11	2.6	29	0.5	14.5
3.5.5[4]	18	0.06	1	0.2	0.2
Total					15.25

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] No animal facility or sponsor has ceased operations to date and none are expected to cease operation in the next several years.
[3] FDA's records indicate that an average of four IND's have been and are expected to be submitted per year.
[4] Has not occurred in the past 5 years and is expected to continue to be a rare occurrence.
[5] Based on 87 patients treated over the last 3 years, the average number of xenotransplantation product recipients per year is estimated to be 29.

TABLE 4.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

PHS Guideline Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
3.2.7 and 4.3[2]	11	1	N/A	16	172
3.4.2[3]	11	15.1	166	3.77	41.5
3.4.3.2[4]	18	4.0	72	1.32	23.8
3.5.1[5]	11	0.09	(0–1) 1	0.045	0.5
3.5.2[5]	11	0.09	(0–1) 1	0.023	0.25
3.5.4	11	2.6	29	0.45	4.9
3.6.4[6]	11	5.3	58	1.32	14.5
3.7[6]	18	3.2	58	0.26	4.6
4.2.3.2[7]	11	27.3	300	4.64	51
4.2.3.2[5]	11	0.09	(0–1) 1	0.015	0.17
4.2.3.3 and 4.3.2[5]	11	0.09	(0–1) 1	0.015	0.17
4.3.1	11	2.6	29	0.66	7.25
5.2[8]	11	7.9	87	0.63	6.96
Total					327.6

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] A one-time burden for setting up a recordkeeping system which rapidly links information regarding the specimen archive, the recipient's medical records, and source animals.
[3] Monitoring for sentinel animals (subset representative of herd) plus all source animals. There are approximately 6 sentinel animals per herd x 1 herd per facility x 18 facilities = 108 sentinel animals. There are approximately 58 source animals per year (see footnote 6 of this table); 108 + 58 = 166 monitoring records to document.
[4] Necropsy for animal deaths of unknown cause estimated to be approximately 4 per herd per year x 1 herd per facility x 18 facilities = 72.
[5] Has not occurred in the past 5 years and is expected to continue to be a rare occurrence.
[6] On average, 2 source animals are used for preparing xenotransplantation product material for one recipient. The average number of source animals is 2 source animals per recipient x 29 recipients annually = 58 source animals per year. (See footnote 5 of table 3 of this document.)
[7] FDA estimates there are approximately 12 clinical centers doing xenotransplantation procedures x approximately 25 health care workers involved per center = 300 health care workers.
[8] Fifty-eight source animal records + 29 recipient records = 87 total records.

Because xenotransplantation is a relatively new area of medical science, potential problems and adverse effects are not well known. Because of the potential risk for cross-species transmission

of infectious agents from source animals to patients, their close contacts, and the general public and the latency period of known human pathogenic persistent virus, the guideline recommends that health records be retained for 50 years. Since these records are medical records, they are not considered ''information'' as that term is defined under the PRA (5 CFR 1320.3(h)(5)). Also, because of the limited number of clinical studies with small patient populations, the number of records is small and, therefore, the capital and operating costs are expected to be insignificant at this time.

Many of the information collections described in this guideline are not new and can be found under existing regulations and, therefore, are not included in the hour burden estimates in tables 1 through 4 of this document. These information collections are included under the regulations and approved under the OMB control numbers as follows: (1) ''Current Good Manufacturing Practice for Finished Pharmaceuticals,'' 21 CFR 211.1 through 211.208, approved under OMB control number 0910–0139; (2) ''Investigational New Drug Application,'' 21 CFR 312.1 through 312.160, approved under OMB control number 0910–0014; and (3) information included in a license application, 21 CFR 601.2, approved under OMB control number 0910–0427. (Although it is possible that a xenotransplantation product may not be regulated as a biological product (e.g., it may be regulated as a medical device), FDA expects, based on its knowledge and experience with xenotransplantation, that any xenotransplantation product subject to FDA regulation within the next 3 years will most likely be regulated as a biological product.)

TABLE 5.—COLLECTIONS OF INFORMATION UNDER CURRENT REGULATIONS

PHS Guideline Section	Description of Collection of Information Activity	21 CFR Section (unless otherwise stated)
2.2.1	Document offsite collaborations.	312.52
2.5	Sponsor ensure counseling patient + family + contacts.	312.62(c)
3.1.1 and 3.1.6	Document well-characterized health history and lineage of source animals.	312.23(a)(7)(iv)(*a*) and 211.84
3.1.8	Registration with and import permit from the Centers for Disease Control and Prevention.	42 CFR 71.53
3.2.2	Document collaboration with accredited microbiology labs.	312.52
3.2.5, 3.4, and 3.4.1	Herd health maintenance and surveillance to be documented, available, and in accordance with documented procedures; record standard veterinary care.	211.100 and 211.122
3.3.3	Validate assay methods.	211.160(a)
3.6.1	Procurement and processing of xenografts using documented aseptic conditions.	211.100 and 211.122
3.6.2	Develop, implement, and enforce SOP's for procurement and screening processes.	211.84(d) and 211.122(c)
3.6.4	Communicate to FDA animal necropsy findings pertinent to health of recipient.	312.32(c)
3.7.1	PHS specimens to be linked to health records; provide to FDA justification for types of tissues, cells, and plasma, and quantities of plasma and leukocytes collected.	312.23(a)(6)

TABLE 5.—COLLECTIONS OF INFORMATION UNDER CURRENT REGULATIONS—Continued

PHS Guideline Section	Description of Collection of Information Activity	21 CFR Section (unless otherwise stated)
4.1.1	Surveillance of xenotransplant recipient; sponsor ensures documentation of surveillance program life-long (justify > 2 yrs.); investigator case histories (2 yrs. after investigation is discontinued).	312.23(a)(6)(iii)(*f*) and (*g*), and 312.62(b) and (c)
4.1.2	Sponsor to justify amount and type of reserve samples.	211.122
4.1.2.2	System for prompt retrieval of PHS specimens and linkage to medical records (recipient and source animal).	312.57(a)
4.1.2.3	Notify FDA of a clinical episode potentially representing a xenogeneic infection.	312.32
4.2.2.1	Document collaborations (transfer of obligation).	312.52
4.2.3.1	Develop educational materials (sponsor provides investigators with information needed to conduct investigation properly).	312.50
4.3	Sponsor to keep records of receipt, shipment, and disposition of investigative drug; investigator to keep records of case histories.	312.57 and 312.62(b)

Dated: 10/10/00
October 10, 2000.

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Margaret M. Dotzel

Margaret M. Dotzel,
Associate Commissioner for Policy.

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